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Albumin in Health and Disease: Causes and Treatment of Hypoalbuminemia

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Abstract

Hypoalbuminemia can be caused by decreased production, increased loss, redistribution, or dilution of albumin. In patients with moderate to severe hypoalbuminemia, fluid accumulation, decreased plasma volume, and thromboembolism may result. Treating the underlying disease process responsible for hypoalbuminemia is the most important factor in managing hypoalbuminemic patients. However, nutritional support, adjustment of medications, prevention of thromboembolism, and maintenance of adequate colloid oncotic pressure are important as well.

Hypoalbuminemia is a common finding in critically ill hospitalized patients.1 When disease leads to moderate or severe hypoalbuminemia (i.e., albumin <2 mg/dl), detrimental consequences may influence the clinical course and negatively impact the prognosis. In fact, multiple human studies and a few veterinary ones have shown hypoalbuminemia to be correlated with a poorer prognosis.2"6 Treatment considerations for hypoalbuminemic patients should address the consequences and cause of hypoalbuminemia. Because hyperalbuminemia is seen clinically only with hemoconcentration and is not a true clinical problem, the focus of this article is the cause and treatment of hypoalbuminemia.

Causes

Causes of hypoalbuminemia can be divided into four general categories: decreased albumin synthesis, increased albumin loss, redistribution of albumin to locations outside the intravascular space, and dilution of albumin within the intravascular space (Figure 1). The cause of hypoalbuminemia in a particular patient is often multifactorial.

Decreased Synthesis

Multiple factors influence albumin synthesis, but clinically relevant decreases in production are typically due to the following: hepatic failure, inflammation, or chronic malnutrition. Because the liver is the primary location of albumin synthesis, hepatic failure resulting in a loss of more than 75% of hepatic function can result in hypoalbuminemia.1 Besides profound failure of hepatocyte synthetic capability, other mechanisms may contribute to hypoalbuminemia in animals with liver dysfunction. In patients with an inflammatory component to their hepatic disease, albumin production can be decreased because of its function as a negative acute-phase protein.2 In patients with cirrhosis and portal hypertension that are causing ascites, newly synthesized albumin is not deposited directly into the systemic circulation and therefore is not measured in serum albumin assays. Instead, a large portion of newly synthesized albumin ends up in the ascitic fluid outside the intravascular compartment. The protein is assumed to leave the hepatic parenchyma and enters the peritoneal fluid via exudation through the capsule of the liver or via hepatic lymphatics.7-9

Inflammation is a well-known cause of hypoalbuminemia. During inflammation, cytokines such as tumor necrosis factor and interleukin-1 serve to shunt amino acids away from producing proteins that are nonessential to the inflammatory process and toward positive acute-phase proteins, including globulins, fibrinogen, and haptoglobin.9 With negative acute-phase proteins such as albumin, the synthetic rate drops during inflammation. The drop in albumin concentration during inflammation can be significant, averaging 0.5 g/dl in humans.2 In rats, albumin synthesis decreased by nearly 60% 24 hours after creation of an iatrogenic abcess.10 In dogs, inflammation can cause mild to moderate hypoalbuminemia.

Malnutrition is often touted as an important cause of hypoalbuminemia. Indeed, many laboratory and clinical studies have shown that albumin synthesis decreases during states of malnutrition. Albumin synthesis decreases by as much as 50% after 24 hours of fasting and is

especially pronounced in situations in which protein malnutrition predominates.2,10,11 However, it is important to note that this decrease in the albumin synthesis capability and concurrent decrease in serum albumin level are clinically apparent only with chronic malnutrition because the capacity of hepatocytes to synthesize albumin quickly normalizes after refeeding.7 In some patients, both nutritional malabsorption and increased intestinal protein loss may contribute to chronic protein malnutrition.9

Increased Loss

The most profound decreases in albumin appear clinically to result from diseases that cause protein loss. Large amounts of albumin may be lost in association with hemorrhage as well as protein-losing nephropathy, enteropathy, and dermatopathy. Hemorrhage results in loss of all constituents of whole blood, including erythrocytes, albumin, and globulin. In general, hypoalbuminemia due to blood loss does not present a diagnostic challenge. Often, the site of blood loss is obvious. Even when the site of loss remains occult, concurrent anemia and hypoglobulinemia should prompt a search for a site of hemorrhage.

Protein-losing nephropathies (e.g., glomerulonephritis or glomerular amyloidosis) result from alteration of the glomerulus with disruption of normal filtering mechanisms. Albumin loss through the normal glomerulus is minimal (0.004%) because despite an effective pore size that is similar to the size of an albumin molecule, there is a strong negative charge to the glomerular basement membrane.10 Negatively charged albumin is repelled from the near equally sized pores. However, in protein-losing nephropathy, the negative charge normally present on the glomeruli is lost and the glomerular pores are widened.12,13 Because larger nonalbumin proteins are retained by the damaged glomerulus, hypoalbuminemia is often accompanied by normal or even elevated serum globulin concentrations. In addition to an increased glomerular loss of albumin, albumin catabolism in the renal tubules may contribute significantly to hypoalbuminemia in patients with protein-losing nephropathy; the mechanism remains poorly understood.2,9,10

Loss of albumin can occur via similar mechanisms in both protein-losing enteropathy and protein-losing dermatopathy. Both disease processes involve large exudative surface areas, whether these areas are in the gut (e.g., severe inflammatory bowel disease) or in the skin (e.g., extensive thermal burns, toxic epidermal necrolysis). The exudative lesions cause loss of all serum proteins simultaneously, resulting in concurrent hypoalbuminemia and hypoglobulinemia. Lymphatic blockage, as occurs in intestinal lymphangiectasia, may also lead to protein-losing enteropathy.9 Because protein-losing enteropathy is usually associated with malabsorption, decreased amino acid uptake and chronic malnutrition may exacerbate the hypoalbuminemic state.

Redistributing Albumin

Albumin is distributed between the extra- and intravascular compartments. Redistribution occurs during diseases that result in inflammation of the vasculature, with widening of the gaps between endothelial cells, such as peritonitis, pleuritis, and vasculitis. The degree of redistribution of albumin from the intra- to extravascular space is likely correlated with the severity and extent of the increase in vascular permeability. In sepsis, for instance, increased vascular permeability allows exaggerated translocation and loss of albumin from the intravascular space. This loss can be measured as the transcapillary escape rate; in humans with septic shock, the transcapillary escape rate can be increased by more than 300%.14 Because compartmental redistribution accompanies inflammatory diseases, the negative acute-phase protein effect is likely a contributing factor to hypoalbuminemia in many of the diseases. Regardless of the cause of increased vascular permeability and redistribution of albumin, the result is a vicious cycle. Translocation of albumin causes intravascular hypoalbuminemia. This, in turn, further increases vascular permeability and causes more intravascular albumin loss.15-17 An explanation of the proposed mechanism of this increase in vascular permeability with hypoalbuminemia can be found in the companion article on page 932 of this issue.

Diluting Albumin

Just as hemoconcentration can result in measured increases in serum albumin concentration, hemodilution can result in minor decreases in serum albumin. Aggressive intravenous fluid therapy can cause such measured decreases. Diseases that result in fluid retention, such as cardiac disease or oliguric/anuric acute renal failure, may also result in dilution of intravascular albumin. For the most part, the minor decreases in albumin concentration attributable to dilution alone do not seem to result in clinical consequences. However, when other causes of hypoalbuminemia are present, dilution of the already decreased serum albumin can have detrimental effects.

Management

Treatment of patients with hypoalbuminemia must be geared toward the primary disease process. However, providing nutritional support, adjusting medications, preventing thromboembolism, and administering colloid support may improve the clinical outcome or even prove lifesaving.

Managing the Underlying Disease

The most important concept in treating hypoalbuminemic patients is to address the underlying problem. Hypoalbuminemia results from underlying disease and is not a disease in itself. If the underlying disease process can be corrected, the albumin level will likely increase and the problems associated with hypoalbuminemia will disappear. Unfortunately, resolution of the diseases known to cause the most profound hypoalbuminemia (i.e., hepatic failure, protein-losing nephropathy, protein-losing enteropathy) is often difficult or delayed. For these cases, supportive measures can be crucial.

Nutritional Support

Nutritional support, particularly providing proteins that supply the amino acid building blocks of albumin synthesis, is vital to the appropriate care of hypoalbuminemic patients. The means by which nutrition is provided depends on the patient's disease. Enteral feeding is preferred to parenteral feeding when the gastrointestinal (GI) tract is functional. Feeding via a nasogastric, esophagostomy, gastrostomy, or jejunostomy tube may be useful for animals that cannot or will not eat enough to meet energy requirements. If enteral feeding is not possible, partial or total parenteral nutrition can be used. Unfortunately, total parenteral nutrition requires placement of a central venous catheter, which may act as a nidus for thrombus formation.

Adjusting Medications

Appropriate dosing of medications that are highly bound to albumin is difficult in hypoalbuminemic animals (for a list of commonly used drugs that are highly bound to albumin, see box on page 934 of this issue). Even in human medicine, specific guidelines for dose adjustment in hypoalbuminemic patients exist for very few medications, and such guidelines are unavailable for most veterinary medications.18 Perhaps the best way to address this problem is to avoid drugs that are highly bound to albumin when possible and to monitor for toxicosis when these medications cannot be avoided.

Preventing Thromboembolism

The necessity of medical therapy and mechanisms used to prevent thromboembolism depends on the individual patient. Low-dose aspirin (for dogs, 0.5 mg/kg PO bid)19 may minimize pathologic platelet aggregation. More efficacious anticoagulants (e.g., warfarin, heparin) may be used when serum albumin is below 2 g/dl, a concentration that has been associated with increased risk of thromboembolism,20 or when evidence of hypercoagulability already exists. When antithrombin (AT) III loss accompanies albumin loss, as is the case in many dogs with protein-losing nephropathy, heparin therapy may not be beneficial. Because heparin works by potentiating the action of ATIII, it cannot be effective in animals deficient in ATIII. A potent alternative to heparin that does not rely on the presence of ATIII is warfarin. Unfortunately, warfarin is highly bound to albumin, resulting in higher free drug concentrations in patients with hypoalbuminemia and a greater risk of bleeding. Warfarin or even heparin therapy requires very close monitoring of patient coagulation times, with the goal of increasing activated partial thromboplastin time by two to two and a half times normal or one-stage prothrombin time by one and a half to two times baseline. Warfarin therapy can have life-threatening consequences and should be reserved for patients at high risk of thrombosis and with scrupulously compliant owners.

Placement of central venous catheters, which are associated with more thrombus formation than are peripheral catheters, should be considered carefully in hypoalbuminemic patients.21 Avoiding the use of catheter types considered to be more thrombogenic (i.e., Teflon, polyvinyl

chloride) and instead using silicon or polyurethane catheters may also help prevent catheter-associated thrombus formation.22,23

Colloid Support

Colloid support can help maintain patient comfort, optimize wound healing, and improve GI motility and absorption in animals with moderate to severe hypoalbuminemia by helping maintain colloid osmotic pressure (COP) and therefore decreasing extravascular fluid accumulation. Unfortunately, administering exogenous colloids to increase COP in animals with hypoalbuminemia can decrease the synthetic rate of albumin.7,8,24 Thus use of colloidal support should be based on clinical evidence of need rather than on the measurement of any arbitrary number. Natural and synthetic colloids are available for use in veterinary species (**Table 1**).

Table 1. Average Molecular Weight, COP, Half-Life, and Dosage of Various Natural and Synthetic Colloidal Solutions Used in Dogs[1,25,32,a]

Solution	Average Molecular Weight (D)	COP (mm Hg)[b]	Half-Life	Dosage
6% Hetastarch	450,000	33	25 hr	10–40 ml/kg/day
6% Dextran 70	70,000	62	25 hr	10–20 ml/kg/day
25% Human albumin	69,000	>200	14–16 days	2 ml/kg[c]
12.5% Human albumin	69,000	95	14–16 days?	4 ml/kg[c]
5% Human albumin	69,000	23	14–16 days?	10 ml/kg[c]
Oxyglobin	200,000	43	30–40 hr	30 ml/kg (one-time dose)
Canine fresh-frozen plasma	Variable (albumin = 69,000)	17	Variable (albumin = 14–16 days?)	10–20 ml/kg over 4–6 hr (or until albumin is >2 g/dl)

[a]Rudloff E, Kirby R: The critical need for colloids: Selecting the right colloids. *Compend Contin Educ Pract Vet* 19(7):811–826, 1997.
[b]Normal canine COP: 14–20 mm Hg.[25,29,34]
[c]Although suggested dosages exist for administering human albumin solution in hypoalbuminemic dogs, it is best to calculate the albumin deficit and administer the necessary amount of albumin using the following formula (the approximate plasma volume in dogs is 40 ml/kg): Albumin (g) = ([Desired albumin − Patient albumin] × Plasma volume × 2) ÷ 100.

The colloidal solution used depends on patient size, cost considerations, disease process, and product availability. Administering any colloidal solution reduces the amount of crystalloid solution necessary by as much as 40% to 60%.25 Therefore, the rate of crystalloid administration should be adjusted accordingly and patients that receive both types of fluids should be monitored carefully for signs of overhydration.

Natural colloids include species-appropriate plasma and human albumin solution. Fresh plasma, fresh-frozen plasma, frozen plasma, and cryosupernatant all increase COP by providing exogenous albumin.26 Large volumes of plasma need to be administered to produce a noticeable increase in serum albumin.27 To increase the albumin level by 0.5 g/dl in a hypoalbuminemic dog, an estimated 22.5 ml/kg of plasma must be administered.1 Because of the need for large volumes of plasma required to replace albumin, veterinarians have used the much more concentrated commercial human albumin solution in dogs.28 Although there are many anecdotal reports on the use of human albumin in dogs, more

research needs to be conducted before routine use of this expensive product can be safely recommended. Because the protein is of human origin, there is potential for immediate or delayed hypersensitivity reactions. Antibody formation to the human protein has not been described in dogs but could be reasonably expected, thereby making repeated transfusions risky. Unfortunately, species-specific albumin is not available for clinical use in veterinary medicine.

Synthetic colloids are much more widely used than natural colloids to increase COP in veterinary species. Hydroxyethyl starch (Hespan, DuPont, Princeton, NJ), high molecular weight dextran, and bovine hemoglobin solution (Oxyglobin, Biopure) have been shown to be safe and effective in dogs.29"31 Parenteral nutrition components have been investigated as potential colloidal solutions.32 However, their contribution to COP is very limited. The availability, safety, and minimal expense of synthetic colloids make them particularly useful in hypoalbuminemic patients. In both humans and veterinary species, using high doses of dextran and hydroxyethyl starch has been associated with increased bleeding times.33,34 This must be considered, particularly in patients treated simultaneously with other anticoagulant drugs or when other primary or secondary hemostatic defects are present.

Regardless of the colloid solution used, serial monitoring of COP using a colloid osmometer is ideal. Serum albumin can serve as a rough estimate of COP when plasma or human albumin is administered for oncotic support but not when synthetic colloids are used. Resolution of peripheral edema and ascites can also be helpful in monitoring the efficacy of colloid solutions in patients with fluid accumulation due to hypoalbuminemia alone.

Colloid support is especially important in patients requiring general anesthesia. Thurman et al35 recommends maintaining a total protein of at least 3.5 g/dl in hypoproteinemic patients undergoing anesthesia. If the total protein cannot be maintained above this level, synthetic colloids should be administered.

In patients with cavitary effusions, removing a portion of the effusion may increase patient comfort. However, because effusions contain varying amounts of albumin, removing the fluid may exacerbate hypoalbuminemia. For patients in respiratory distress or discomfort due to significant amounts of ascites or pleural effusion, removing just enough effusion to normalize respiration is recommended.

Conclusion

Regardless of the underlying cause of hypoalbuminemia, management should focus on addressing the underlying disease. Preventing the various consequences of hypoalbuminemia and providing supportive care are also important. Specific treatment should be tailored to the patient's unique needs and problems.

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